

Renal venous thrombosis in neonates: prothrombotic risk factors and long-term follow-up

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The present study was designed to evaluate prothrombotic risk profiles in 59 consecutively recruited white neonates with renal venous thrombosis (RVT). The rates of prothrombotic risk factors (PRs)—for example, the factor V (FV) 1691G>A mutation, the factor II (FII) 20210G>A variant, antithrombin (AT), protein C (PC), protein S (PS), elevated lipoprotein(a) (Lp(a)), total fasting plasma homocysteine (tHcy) levels, and anticardiolipin antibodies (ACAs)—were compared with those of

118 healthy control children. At onset, 32 (54.2%) of the 59 neonates showed underlying clinical conditions; 40 (67.8%) of them and 23 (85.2%) of the 27 infants with idiopathic RVT showed at least one PR. Univariate analysis revealed significantly elevated odds ratios/95% confidence intervals (ORs/95% CIs) for FV and Lp(a). Additionally, PC/AT deficiency and ACAs were found significantly more often in the patient group ($P = .04$). Multivariate analysis calculated significant ORs/95% CIs

only for FV (OR, 9.4; 95% CI, 3.3-26.6) and elevated Lp(a) (OR, 7.6; 95% CI, 2.4-23.8). Of the 59 neonates investigated, 53 revealed renal atrophy, and 13 children additionally suffered from severe arterial hypertension. In conclusion, the present study demonstrates the significance of genetic PR—especially the FV mutation and elevated Lp(a)—for the etiology of neonatal RVT. (Blood. 2004;104:1356-1360)

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Introduction

Renal venous thrombosis, although rare in adults, is a well-recognized and potentially fatal entity in children and neonates.¹ Renal venous thrombosis (RVT) is by far the most common manifestation of neonatal thrombosis: The overall incidence of thromboembolic events in the neonatal period is 5 per 100 000 births; more than 40% of all thrombotic manifestations in this age group are symptomatic RVTs.^{2,3} Persisting impairment of kidney function and the need for renal replacement therapy are serious and common complications in patients with RVT.⁴

Renal venous thrombosis occurs predominantly in the neonatal period, and the incidence decreases significantly after the first year of life. It may present with a clinically palpable enlargement of the kidney in association with hematuria, proteinuria, renal failure and oliguria, hypertension, or thrombocytopenia. Long-term functional impairments include hypertension and renal insufficiency.^{4,5} Many imaging modalities have been employed, but ultrasound and color Doppler ultrasound are the techniques most commonly used in the evaluation of neonates with suspected RVT.⁶

Although the etiology of RVT is not fully understood, predisposing factors for neonatal RVT include dehydration, sepsis, birth asphyxia, polycythemia, maternal diabetes, traumatic delivery, congenital renal vein defects, and an indwelling umbilical venous catheter.^{7,8} Little is known of the role of inherited prothrombotic risk factors (PRs) in the development of spontaneous or exog-

enously triggered RVTs in children. We have previously shown that the factor V 1691G>A (Leiden) mutation and further hereditary prothrombotic risk factors are strong determinants of thromboembolic complications in pediatric patients.⁹⁻¹⁴ However, the role of these risk factors in the pathogenesis of neonatal renal venous thrombosis is not clear so far. Moreover, the published studies on this disease are sparse, and follow-up data on the functional outcome after neonatal RVT in larger numbers of patients are lacking.^{3,15,16}

Therefore, we performed a multicenter case-control study to assess to what extent single or combined thrombophilic risk factors influence the onset of neonatal renal venous thrombosis in Germany. The follow-up and outcome of these children was additionally studied on an exploratory basis.

Patients, materials, and methods

Ethics

The present study was performed in accordance with the ethical standards laid down in the updated relevant version of the Declaration of Helsinki and was approved by the medical ethics committee at the Westfälische Wilhelms-University, Münster, Germany.

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A complete list of the members of the Childhood Thrombophilia Study Group appears in the "Appendix."

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Patients

White patients with a first symptomatic renal vein thrombosis in the neonatal period were consecutively recruited since January 1989 by the participating centers in the catchment areas of Hamburg, Kiel, Lübeck, Münster, Bielefeld, Düsseldorf, Berlin, Magdeburg, Halle, Frankfurt, and Munich, Germany, and screened for hereditary prothrombotic risk factors between January 1996 and June 2003.

Inclusion/exclusion criteria

Inclusion criteria were a symptomatic RVT in the neonatal period confirmed objectively by standard imaging methods. Children older than 28 days at RVT onset and patients with no parental consent were not enrolled in the present study. In addition, owing to the lack of adequate pediatric controls, children with RVT and incomplete prothrombotic workup of established PRs ($n = 35$) recruited from 1989-1995 (when factor V [FV] 1691G>A, FII 20210G>A, elevated lipoprotein (a) [Lp(a)] were not routinely investigated) were not included in the case-control analysis. However, since the 2 consecutively enrolled cohorts were no different with respect to enrollment criteria, clinical presentation, distribution of term and preterm neonates, associated underlying diseases, anticoagulant/antithrombotic therapy, and diagnostic and imaging follow-up procedures, the entire population of 94 children was studied with respect to recurrent thromboembolism (study end point) on an exploratory basis.

Control group

Patients were compared with 118 healthy neonates from different geographic areas of Germany. Controls were recruited between January 1996 and June 2003. They comprised children with no history of chronic disease or of thromboembolic events, without any medication at the time of recruitment, and who presented as outpatients for evaluation before minor surgery (planned circumcisions and hernias) or bone marrow donation.

Imaging methods used at thrombotic onset, follow-up, and suspected rethrombosis

The methods used were color duplex sonography,^{2,6,17-19} venography, computed tomography (CT) or magnetic resonance (MR) imaging for the diagnosis of venous thromboembolism; and cerebral CT scanning, MR imaging, MR angiography, or transcranial Doppler ultrasonography for the diagnosis of thromboembolic ischemic stroke.¹² Ultrasound criteria for diagnosis of RVT included echogenic clot visibility, venous distension by the thrombus, absence of flow by color or pulsed Doppler scanning, and the lack of flow augmentation. In children with renal venous thrombosis and suspected renal impairment during the follow-up, renal scintigraphy was also performed.

Predefined underlying clinical conditions

As described recently,²⁰ bacterial or viral infections, vascular trauma, surgery, macrosomia, jugular or central lines, solid tumors, autoimmune diseases, renal diseases, metabolic disorders, birth asphyxia, and cardiac malformations were predefined as predisposing clinical conditions in the ongoing multicenter study. In addition, drugs such as steroids and the use of sympathomimetics and coagulation factor concentrates were classified as underlying conditions. Patients suffering from RVT but not showing any of the criteria stated here were classified as idiopathic.

Laboratory tests

With parental consent, the FV GA and FII GA mutations, resistance to activated protein C, concentration of Lp(a), protein C (PC), protein S (PS), antithrombin (AT), total fasting plasma homocysteine (tHcy) levels, and anticardiolipin antibodies (ACAs) were routinely investigated in German patients and controls recruited since 1995 by means of standard laboratory techniques at the time of diagnosis and 3 to 6 months after acute thrombotic onset.^{20,21} Beyond the acute event, laboratory analyses were confirmed in the pediatric coagulation laboratory and pediatric molecular hemostasis

laboratory of the Department of Pediatric Hematology and Oncology of the University of Münster, Germany as the reference laboratory for the ongoing multicenter study. A type I deficiency (antithrombin, protein C) was diagnosed when functional plasma activity and immunologic antigen concentrations of a protein were repeatedly shown to be below 50% of the normal age-related limit.²² A type II deficiency (antithrombin, protein C) was diagnosed in patients with repeatedly low functional activity along with normal antigen concentrations. The diagnosis of protein S deficiency was based on reduced free protein S antigen levels combined with decreased or normal total protein S antigen concentrations. For ACAs (Vareliisa cardiolipin antibodies immunoglobulin G [IgG]/IgM) (Pharmacia Diagnostics, Freiburg, Germany), cutoff values greater than 20 IU/mL (IgG) and greater than 11 IU/mL (IgM) were considered abnormal. Serum levels of Lp(a) greater than 0.3 g/L (30 mg/dL) were considered elevated, and 28 kringle IV repeats were used as the cutoff for the definition of small apolipoprotein(a) (apo(a)) isoforms. The tHcy levels were measured in EDTA (ethylenediaminetetraacetic acid) plasma by high-performance liquid chromatography (HPLC) with reverse phase separation and fluorescent detection based on the method of Araki and Sako.²³ Plasma tHcy above 10 μ M was regarded as elevated.²⁴ Criteria for the hereditary nature of a hemostatic defect were its presence in at least one first-degree family member, the identification of a causative gene mutation, or both.

Clinical routine procedures performed by the participating centers

Besides the prothrombotic testing mentioned before, the routine diagnostic tests after renal venous thrombosis performed 6 weeks, 3 months, 6 months, 12 months, and 2 years after initial hospital discharge include physical examination; serial oscillometric blood pressure recordings; urine analysis; a plasma biochemical profile, including plasma creatinine; and imaging methods (ultrasound, Duplex or color Doppler ultrasound, MRI, and renal scintigraphy, which was performed only in the patients with suspected impaired renal function).²⁵⁻²⁷ After the initial 2-year follow-up, patients were examined again after 5 to 10 years depending on the degree of renal function impairment.

Statistical analysis

All statistical analyses were performed with the StatView 5 software package (SAS Institute, Cary, NC) and the MedCalc software package (MedCalc, Mariakerke, Belgium). To compare the rate of prothrombotic risk factors in patients and controls, to evaluate an independent contribution of thrombophilia to the onset of RVT, and to adjust for the possible interaction of combined prothrombotic risk factors, the odds ratios (ORs) together with 95% CIs were estimated from a multivariate analysis by means of a logistic regression model.

Prevalences of prothrombotic risk factors in patients and control subjects were calculated by χ^2 analysis or, where relevant, by Fisher exact test. The significance level was set at 0.05.

Results

Final study population (case-control study)

From the ongoing multicenter study, the subgroup of 59 out of 94 children with neonatal RVT was analyzed in a case-control design. In this cohort of children suffering neonatal RVT, symptomatic venous thrombosis was present in 7 parents (5.9%) before the age of 35 years, and in 1 sister before the age of 18 years.

For the case-control study 24 female and 35 male patients with confirmed RVT were enrolled. Forty-five affected patients were term neonates (median, 40 gestational weeks; range, 37-42 gestational weeks), and 14 were premature patients (median, 31 gestational weeks; range, 25-36 gestational weeks). Interestingly, the female-male ratio was shifted toward a male predominance (1:1.5).

Table 1. Distribution of single and combined prothrombotic risk factors in neonatal patients at RVT onset, in recurrent thrombosis, and in healthy controls

Prothrombotic risk factor	Onset of renal venous thrombosis, no./sample size (%); n = 59	Recurrent thrombosis in carriers, no./sample size (%); n = 4	Control group, no./sample size (%)
Factor V 1691G>A, total	22/59 (37.3)	2/22 (9.1)	7/118 (5.9)
Homozygous A1691A	1	1	0
Single heterozygous 1691G>A	13	0	7
With lipoprotein(a) greater than 0.30 g/L	5	1	0
With factor II	2	0	0
With protein C deficiency	1	0	0
Factor II 20210G>A, total	5/59 (8.5)	0/5 (0)	2/118 (1.7)
Single	0	0	2
With factor V 1691G>A	2§	0	0
With lipoprotein(a) greater than 0.30 g/L	3	0	0
Lipoprotein(a) more than 0.3 g/L, total	17/59 (28.8)	1/17 (5.9)	5/118 (4.2)
Single	6	1	5
With factor V 1691G>A	5§	(1)§	0
With factor II	3§	0	0
With Hcy greater than 10 μ M*	1	0	0
Protein C deficiency, total†	3/59 (5.0)	1/3 (33.3)	0
Single	2	1	0
With factor V 1691G>A	1§	0	0
Antithrombin deficiency, total‡	3/59 (5.0)	0	0
Single	3	0	0
ACAs greater than 2 SDs, total	3/59 (5.0)	0	0
Single	3	0	0

Breakdown for prothrombotic risk factors was as follows: single, n = 28; combined, n = 12.

*19 μ M Hcy (6 to 12 months after acute onset; confirmed in at least one family member; methylenetetrahydrofolate reductase [MTHFR] 677C>T).

†5%, 7%, and 12%.

‡5%, 12%, and 20%.

§This entry refers to the same data as an earlier table entry.

Leading symptoms at onset of symptomatic renal venous thrombosis

Hematuria and thrombocytopenia were the leading symptoms in 29 of the 59 neonates (49.1%). In 16 children (27.1%), anuria had occurred, and 9 subjects (15.3%) presented with a palpable abdominal mass. In 5 neonates (8.5%), adrenal bleeding was observed.

Thrombotic locations

Twenty-three neonates (38.9%) presented with a left renal vein thrombosis; 20 (33.9%) with right-sided thrombosis; and 16 (27.2%) with bilateral RVT. In 15 of these patients (25.4%), an additional thrombosis of the inferior caval vein was present. Further venous thromboses (deep venous thrombosis, n = 2; hepatic vein, n = 1; and pulmonary embolism, n = 1) or arterial occlusions (ischemic stroke, n = 4; aorta, n = 1; mesenteric artery, n = 1) were diagnosed at symptomatic thrombotic onset.

Additional underlying clinical conditions

RVT occurred spontaneously in 27 children (45.8%) without any underlying clinical conditions predefined in the "Patients, materi-

als, and methods." In the remaining children, sepsis (n = 10), the use of central venous lines (n = 9), birth asphyxia (n = 7), maternal administration of betamethasone (n = 4), and diabetic fetopathy (n = 2) were associated with the onset of neonatal RVT.

Acute antithrombotic treatment

At the discretion of the participating study centers, patients were treated with low-molecular-weight heparin (LMWH) (2- to 4-hour anti-factor Xa level, 0.4 to 0.6 IU/mL) or unfractionated heparin (UFH) (activated partial thromboplastin time [aPTT] increase, 1.5- to 2-fold compared with baseline). Intravenous thrombolysis was performed with rt-PA according to doses given in Nowak-Göttl et al.²⁸

Of the 59 subjects affected, 28 (47.5%) were treated with low-molecular-weight heparin, 5 (8.5%) with unfractionated heparin, and 4 (6.8%) with antithrombin concentrates, while another 11 (18.6%) underwent intravenous thrombolytic therapy. In addition, 18.6% (11 of 59) received only supportive treatment but no antithrombotic therapy. In accordance with our previously published data,³ however, acute antithrombotic treatment was not associated with the clinical outcome reported by the participating study centers ($P = .3$).

Distribution of prothrombotic risk factors

In 40 (67.8%) of the 59 patients, at least 1 established prothrombotic risk factor was found compared with 14 (11.9%) in the 118 control children (OR, 15.6; 95% CI, 7.2-34.2). The distribution of single and combined prothrombotic risk factors in patients is shown in Tables 1 and 2.

Upon univariate analysis comparison with controls, patients showed significantly a higher prevalence of FV 1691G>A (OR, 11.1; 95% CI, 4.2-29.5) and elevated Lp(a) (OR, 9.2; 95% CI, 3.2-26.4). Additionally, protein C deficiency ($P = .04$), antithrombin deficiency ($P = .04$), and increased ACAs (in all cases more

Table 2. Interaction between prothrombotic risk factors and underlying clinical condition (UCC)

Prothrombotic risk factor	Onset of renal venous thrombosis, no./sample size (%)	Recurrent thrombosis in carriers, no./sample size (%)
PR		
With UCC	18/59(30.5)	2/18(11.1)
Without UCC	22/59(37.3)	2/22(9.1)
No PR		
With UCC	15/59(25.4)	0(0.0)
Without UCC	4/59(6.8)	0(0.0)

than 2 standard deviations [SDs] above the mean; $P = .04$) were significantly more common in the patient group, with 3 cases of each detected. No significant differences were found for frequencies of FII 20210G>A (OR, 4.3; 95% CI, 0.8-24.2); protein S deficiency was not diagnosed in either the patient or the control population investigated. In a multivariate analysis that included all the prothrombotic risk factors significantly associated with RVT in the univariate analysis (FV 1691G>A, elevated Lp(a), protein C and antithrombin deficiency, presence of increased ACAs), only the heterozygous FV mutation (OR, 9.4; 95% CI, 3.3-26.6; $P < .0001$) and elevated Lp(a) (OR, 7.6; 95% CI, 2.4-23.8; $P = .0005$) retained their statistically significant association with symptomatic neonatal RVT. Interestingly, 22 (81.5%) of 27 neonates with idiopathic RVT showed at least one PR. The distribution of single and combined prothrombotic risk factors was not associated with long-term renal impairment ($P = .6$).

Outcome

The primary aim of this study was to evaluate the rate of prothrombotic risk factors as an underlying condition in neonatal RVT patients. However, information is also available on the long-term clinical outcome. During the follow-up period, 53 (89.8%) of the 59 neonates with RVT (heparin group, 30 of 33; antithrombin group, 4 of 4; thrombolysis group, 9 of 11; supportive therapy, 10 of 11) revealed relevant unilateral renal atrophy on ultrasound scan in 42 cases, and bilateral renal atrophy in 11 subjects. In 3 (27.3%) of the 11 children with bilateral RVT and bilateral organ damage, a renal transplantation was necessary. Ten children with unilateral atrophy and the 3 children with bilateral atrophy before transplantation suffered from severe arterial hypertension, necessitating long-term antihypertensive treatment. In one girl, a nephrectomy had to be performed at the age of 2 because of extensive arterial hypertension.

Recurrent thromboembolism (exploratory study)

The median follow-up time was 4.0 years (range, 0.6-15.0 years), and 4 (4.3%) of the 94 children with neonatal RVT suffered a second thromboembolism. Interestingly, in 3 of the 4 cases, a second symptomatic thrombosis occurred during puberty. No patient received secondary prophylactic antithrombotic treatment at the time of recurrence. All patients with recurrent events had at least one prothrombotic defect (single PR, $n = 2$; combined PR, $n = 2$).

Discussion

The present multicenter case-control study was designed to assess the extent to which single and combined clotting factor abnormalities influence the onset of neonatal renal venous thrombosis in Germany and, furthermore, to evaluate on an exploratory basis renal impairment and recurrent symptomatic venous thrombosis.

Data presented here clearly demonstrate that prothrombotic risk factors were observed significantly more frequently in patients with RVT than in healthy control children. Besides the genetic thrombophilic risk factors—for example, the FV 1691G>A mutation, the FII 20210G>A variant, elevated concentrations of Lp(a), protein C deficiency, and antithrombin deficiency—acquired increased ACAs were also involved in the first thrombotic onset in the neonatal period. Our data support case reports by Leret et al¹⁶ and Giordano et al¹⁵ demonstrating that RVT in neonates is associated with the heterozygous FV 1691G>A alone or in combination with further PR, such as the heterozygous FII 20210G>A variant.

On the one hand, when the number of single and combined prothrombotic risk factors are taken into account, logistic regression as a multivariate statistical model clearly demonstrates that the FV 1691G>A mutation and elevated Lp(a) concentrations are significant and independent risk factors for the development of RVT in neonates. On the other hand, as a limitation of the present study, no conclusion can be drawn from the data presented here with respect to PRs' not reaching statistical significance: thus, to clarify the role of the FII 20210G>A variant; of deficiencies in protein C, protein S, and antithrombin; and increased homocysteine and ACAs; further international studies performed in white children are recommended to increase the statistical power.

Besides the role of inherited or acquired thrombophilia as an underlying pathomechanism of RVT in the neonate, data of the present study also suggest that renal venous thrombosis in children is a multifactorial disease: The existence of underlying disorders—for example, asphyxia, sepsis, diabetic fetopathy, central lines, or the administration of prenatal betamethasone—in combination with prothrombotic risk factors also appear to play a major role in the pathogenesis of the event. In addition, in accordance with previously published data, we observed more affected male than female newborns.^{3,29}

Although the present study focused mainly on the role of thrombophilia at the onset of neonatal RVT, preliminary follow-up data suggesting a poor long-term outcome are available. Only 6 of 59 neonates with RVT in our study showed no organ damage in the follow-up investigation. These data are in accordance with smaller series with a poor outcome after RVT^{25,30,31}: Keidan and coworkers³⁰ observed complete atrophy of the affected kidneys in 4 of 6 affected neonates after RVT, and in a follow-up study Mocan et al²⁵ reported a normal ultrasound of the kidney in only 2 of 14 RVT patients studied. Renal impairment was not associated with the presence of prothrombotic risk factors or the acute anticoagulant/antithrombotic treatment performed. Since no evidence-based guidelines are available so far with respect to acute antithrombotic treatment of neonates suffering RVT, treatment modalities varied among the participating study centers. The variations in treatment and the fact that in the present study no randomization of antithrombotic drugs was performed have to be discussed as further limitations of the study presented here. Although no statistical correlation was found between renal impairment and acute anticoagulant/antithrombotic therapy during the follow-up, this issue needs to be addressed in further prospective intervention studies.

In 4 of 94 patients (the entire cohort) a recurrent thromboembolic event occurred during the follow-up period. Interestingly, 3 of 4 events occurred during puberty, a time point also known as the second peak for childhood thrombosis.³² In addition, none of the 4 patients received secondary prophylactic antithrombotic treatment at the time of recurrence. The recurrence rate of 4.3% in the cohort presented here with a median patient follow-up of 4 years represents only the tip of the iceberg, and the appropriate incidence of recurrence will be manifest within the next 10 to 15 years when the majority of children enrolled in the present study have passed puberty. In accordance with our previously published data,¹¹ 2 (16.7%) of the 12 children with neonatal RVT with combined PRs suffered a recurrent thrombotic event, suggesting that the presence of combined hereditary risk factors also significantly increases the risk for recurrence of venous thrombosis in patients with RVT.^{11,33}

In conclusion, the present study demonstrates the significance of genetic prothrombotic risk factors—especially the FV 1691G>A mutation and the elevation of Lp(a)—for the etiology of renal venous thrombosis in white neonates. On the basis of the data presented here

and the fact that the family history was positive for venous thrombosis in 11.9% of cases, screening for thrombophilic risk factors—for example, the FV 1691G>A mutation, the FII 20210G>A variant, Lp(a), protein C, protein S, antithrombin, and ACAs—is recommended in white neonates with RVT. To our knowledge, no controlled data are available with respect to the interaction between PR and neonatal RVT in nonwhite children. Therefore, this screening recommendation is restricted to white patients only. Since secondary antithrombotic treatment is available in at-risk situations, such as immobilization or surgery, a screening for prothrombotic risk factors after neonatal RVT may help to stratify the risk of recurrence.¹¹ Besides controlled, randomized, multicenter studies to clarify the role of prothrombotic risk factors that did not reach significance in the cohort investigated here, further international trials are needed to prospectively examine the benefit of different acute and secondary anticoagulant/antithrombotic treatment strategies.

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